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Parity and Down Syndrome

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Previous studies have suggested a positive correlation between grand multiparity and the incidence of Down syndrome (DS). In order to study different parities as risk factors for DS, the Swedish health registries were used, and 2,615 infants with Down syndrome were selected from 2,184,590 infants born in 1973–1993. A statistically significant risk decrease for primiparas, and a significant risk increase for grand multiparas (5+), was found (age-adjusted odds ratios: 0.87 (95% CI: 0.80–0.96) and 1.40 (95% CI: 1.18–1.65), respectively. Potential confounders, such as the effect of truncated maternal 1-year age classes, citizenship, socioeconomic level, etc., were evaluated but were found to have only marginal effects. Evidence suggesting that the extension of prenatal diagnosis during the study period has decreased the incidence of DS among women of parity 1–4, but not among women of parity 5+, was found. The hypothesis that Swedish grand multiparas may have another attitude toward prenatal diagnosis than women of lower parities was confirmed when, in a data set containing information on 872 amniocenteses, a significantly lower rate of grand multiparity than expected was found. For the negative association between primiparity and DS, no obvious confounder was found. Am. J. Med. Genet. 70:196–201, 1997. © 1997 Wiley-Liss, Inc.

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INTRODUCTION

The epidemiology of Down syndrome (DS) has been studied intensively during the past decades, but the only association with DS that has been unequivocally proven is the well-known maternal age effect on Down rates.

In 1988, Källén and Måsbäck found that parity seemed to play a role in the incidence of DS. They found a significantly lower risk for primiparas to have an infant with DS than for 2+-paras, notably at higher maternal age classes. They also described that parity 1 (but not parity 2+) DS mothers had some characteristics which distinguish them from age-matched controls, e.g., fewer previous induced abortions. Stoll et al. [1990] also found that first-born infants were at lower risk of DS than the later-born, a finding that did not agree with a report of Hook [1981], who found an increased risk of DS among first-born infants.

In a letter, Fishman [1994] refers to a possible association between grand multiparity and DS reported by Schimmel et al. [1994], who found an additional 15% risk for women with 6 children or more to give birth to an infant with DS. In a letter by Castilla and Paz [1994], almost the same risk increase (14%) for grand multiparous women to have infants with DS was reported, but these authors found evidence that suggested that their finding was due to truncation of maternal age. Haddow and Palomaki [1994] found no significant association between DS and parity after adjustment for maternal age.

By using the Swedish health registries (the same source as used by Källén and Maåsbäck [1988] but for an extended study period), the relation between parity and DS was further investigated.

MATERIAL AND METHODS

Infants with DS, born in 1973–1993, were identified from five registries: The Swedish Registry of Congenital Malformations (RCM), the Cytogenetic Registry, the Child Cardiology Registry, the Registry of Handicapped Children, and the National Board of Health Medical Birth Registry (MBR). These registries and the techniques to use them in epidemiological studies have been described in detail elsewhere [Källén and Winberg, 1979; Lindsten et al., 1981; Källén, 1987; Cnattingius et al., 1990].

Every fifth year, information on all Swedish citizens is collected based on a census and is computerized into a registry. By linking the census registry with the MBR, information on maternal socioeconomic index (which is an estimate of educational level based on current occupation) could be obtained for infants born during 1981, 1986, and 1991. In this report, the following division of socioeconomic status was made from the socioeconomic index: 1) academics, 2) skilled workers, 3) unskilled workers, 4) no work outside home.

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Since the introduction (in the late seventies) of prenatal diagnosis, the rate of amniocentesis has steadily increased, and since 1993 free prenatal diagnosis is offered to women 35 years or over in most Swedish counties. The effect of prenatal diagnosis on the incidence of DS within different parity groups cannot be studied directly, as no nationwide registration of prenatal diagnoses for the relevant time period exists. Instead, a data set containing information on 1,061 amniocenteses performed in the southern counties of Sweden during 1992 (corresponding to 18% of the total number of amniocenteses in Sweden that year) was available. All prenatal diagnoses carried out with an indication other than "unspecified anxiety" or maternal age ⩾35 years were sorted out, leaving 872 records of amniocenteses to be linked with MFR (to obtain information on parity and municipality of residence), and analyzed. As the likelihood for a woman to undergo prenatal diagnosis may depend on the distance between home and hospital, stratification for municipality of residence was made in the analysis of parity and amniocentesis.

The gradual extension of prenatal diagnosis, and the changes in the maternal age distribution in pregnant Swedish women, made it necessary to consider year of birth as a confounder when studying a possible association between DS and parity.

All odds ratios presented in this report were calculated using Mantel-Haenszel's technique [1959]. Stratification was made for year of birth and maternal age (1-year classes). Ninety-five percent confidence intervals (CI) were estimated using Miettinen's method [1974]. When comparing two stratified odds ratios, two-tailed z-tests were carried out, using the same variance as used to estimate the 95% CI.

A regression analysis was performed to describe the relation between maternal age (x) and frequency of DS (y), using the model $y = \exp(c1 + c2 * x + c3 * x^2)$, where c1, c2, and c3 are constants.

An analysis of variance was used to investigate the mean ages within each of the one-year maternal age classes among mothers of DS infants and controls (total population), grand multiparas (5+) and 1–4-paras.

The infants with DS were divided into trisomies, mosaics, translocations, and unknown type of chromosome anomaly causing DS. However, the numbers of infants in the mosaics and translocations groups were not sufficient to estimate odds ratios among different parities with reasonable precision. No further analysis of the individual groups are therefore presented in this report.

TABLE I. Number of Infants With Down Syndrome and Controls According to Maternal Age and Parity

	Down syndrome		Total population	
	< 35 years	⩾ 35 years	35 years	⩾ 35 years
Parity 1	684	107	885,958	35,099
Parity 2	725	205	728,759	59,286
Parity 3	309	222	274,936	62,779
Parity 4	74	121	64,983	31,863
Parity 5+	23	145	20,391	20,536
Total	2,615		2,184,590	

TABLE II. Odds Ratios With 95% CI for Down Syndrome for Each Parity Group as Specified vs. All Other Parities After Stratification for Maternal Age (1-Year Classes) and Year of Birth

	All maternal ages	< 35 years	⩾ 35 years
Parity 1	0.87 (0.80–0.96)	0.89 (0.81–0.99)	0.81 (0.66–0.99)
Parity 2	1.06 (0.98–1.15)	1.10 (1.00–1.21)	0.97 (0.83–1.15)
Parity 3	1.01 (0.91–1.11)	1.04 (0.91–1.18)	0.96 (0.82–1.12)
Parity 4	0.92 (0.79–1.07)	0.96 (0.76–1.21)	0.89 (0.73–1.08)
Parity 5+	1.40 (1.18–1.65)	0.89 (0.59–1.35)	1.56 (1.30–1.88)

RESULTS

Table I shows the number of infants with DS according to maternal age and parity.

Table II shows odds ratios and their 95% CI for DS among different parity groups vs. all other parities according to maternal age (<35 years and ⩾35 years) after stratification for maternal age (1-year classes) and year of birth. Among primiparas, the odds ratios are significantly below unity within all age groups. Among parity groups 2, 3, and 4, the OR for DS is about unity within both age groups. For parity group 5+ (grand multiparas), the OR is significantly increased among women ⩾35 years of age, whereas among women <35, the OR is slightly decreased. The difference in the magnitude of the association between DS and parity 5+ between these age groups is statistically significant ($P = 0.015$). The group of grand multiparas was further divided into 5-para and 6+-para. No difference in the magnitude of the association with DS between those two groups was demonstrated. Table III shows OR for parity 1 and parity 5+, respectively, when parity groups 2–4 (instead of all other parity groups) were used as a reference. The change in the reference group definition did not substantially alter the results shown in Table II.

Replacement Pregnancy Phenomenon

Death of an infant often results in a replacement pregnancy, thereby increasing parity. In order to investigate whether the association between multiparity and DS could be related to the "replacement pregnancy" phenomenon, information on the outcome of previous pregnancies of 5+-paras was gathered and analyzed. Among 117 infants with DS, 8 had one previously born sib that had died and/or was born with a major congenital malformation. For controls, the corresponding numbers were 31,061 and 1,945, respectively. The resulting OR for multiparous mothers of DS children to have had previous adverse outcomes of

TABLE III. Odds Ratios With 95% CI for Down Syndrome for Parity 1 and Parity 5+ vs. Parity Groups 1–4, After Stratification for Maternal Age and Year of Birth

	All maternal ages	< 35 years	⩾ 35 years
Parity 1	0.89 (0.81–0.97)	0.89 (0.80–0.99)	0.86 (0.70–1.07)
Parity 5+	1.36 (1.14–1.61)	0.86 (0.57–1.31)	1.52 (1.26–1.84)

pregnancies vs. multiparous control mothers (after stratification for year of birth and maternal age) was 1.08 (0.49–2.40). This analysis was based on too few cases of dead and/or malformed sibs to estimate the OR for DS with reasonable precision, but it can be stated that the phenomenon of replacement pregnancies is unlikely to be an important contributor to the observed association between multiparity and DS.

Changes Over the Study Period

Figure 1 shows regression lines for the incidence of DS according to maternal age, time period, and parity. The introduction (during the late seventies) of prenatal diagnosis in pregnant Swedish women 35 years or older has decreased the number of children with DS born to women in this age group. However, Figure 1 shows that among multiparas, no decrease of the incidence of DS has occurred. In order to study a putative change in the magnitude of multiparity as a risk factor for DS over the years 1973–1993, the OR (after stratification for maternal age and year of birth within each period) for DS according to parity and time period was calculated (Fig. 2). A negative association between parity 1 and DS is indicated in all study periods and in both age groups, although the significance disappears when division into time period periods is made. The size of the positive association between grand multiparity and DS among women ⩾35 years is impressive, but is demonstrated only in the two latter study periods.

Prenatal Diagnosis

In the absence of nationwide registration of prenatal diagnoses for the relevant time period, the data set mentioned above with information on amniocentesis taking place in the south of Sweden in 1992 was analyzed. The OR after stratification for maternal age and community of residence for amniocentesis among 5+-paras vs. all other parities was 0.60 (95% CI: 0.43–0.84). Among 1-paras and 2–4-paras the corresponding ORs were 1.14 (95% CI: 0.94–1.39) and 1.06 (95% CI: 0.89–1.26), respectively.

In order to describe the group of multiparous mothers, a further analysis was made.

Socioeconomic Index (SEI)

Information on maternal SEI could only be obtained for infants born in 1981, 1986, or 1991. Among the group of grand multiparous women, the percentages of SEI groups 1–4, as defined previously, were 2.5%, 11%, 31%, and 55%, respectively. The corresponding per-

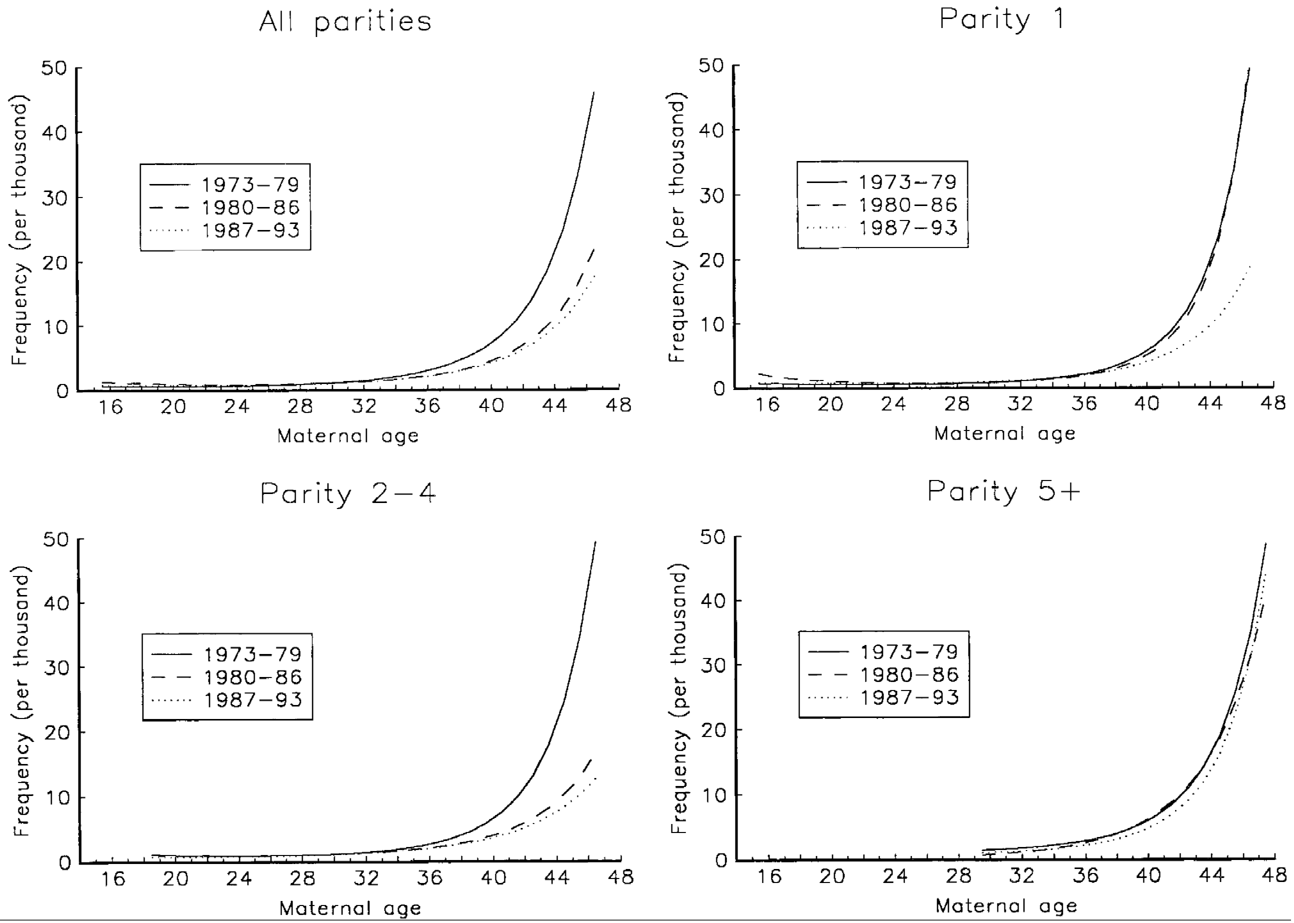

Fig. 1. Frequency of Down syndrome in Swedish infants according to maternal age and parity during the three time periods specified. The regression lines were computed using the model y = exp (c1 + c2 ∗ x + c3 ∗ x^2), where y = frequency, x = maternal age, and c1, c2, and c3 are constants.

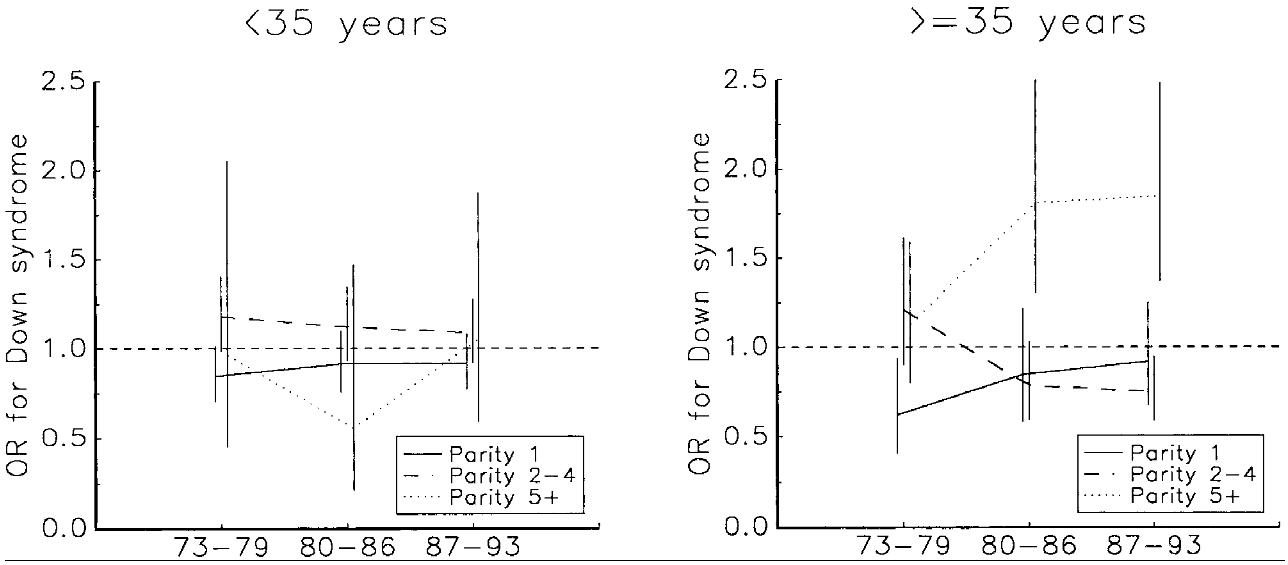

Fig. 2. Odds ratios with 95% CI for Down syndrome after stratification for maternal age (1-year classes) and year of birth, according to parity, time period, and maternal age group.

centages in the total population were 5%, 32%, 39%, and 23%, respectively. The ORs for DS among SEI groups 1–4 vs. all other SEI groups were estimated after stratification for maternal age, year of birth, and parity. Among women <35 years old, no significant effect of SEI was demonstrated. Among women 35 years or over the ORs for SEI groups 1–4 were 1.48 (0.90–2.44), 0.57 (0.38–0.87), 1.36 (0.91–2.04), and 1.03 (0.68–1.57), respectively. Within each of the four SEI groups, the OR for DS was below unity among primiparas. Within SEI groups 1 and 2 (academics and skilled workers, respectively), grand multiparity is rare, and no OR for DS could be estimated. Within SEI groups 3 and 4 (workers and housewives), the OR for DS among children born to grand multiparous mothers 35 years or older were 1.92 (0.90–4.12) and 1.57 (0.70–3.54), respectively.

Citizenship

In order to study whether multiparous women were to a high extent immigrants and (because of religious, cultural, or other reasons) were perhaps less likely to accept prenatal diagnosis than Swedish women, and whether this might have contributed to the observed association between grand multiparity and DS, information on nationality among all cases and references was gathered and analyzed. Nine percent of grand multiparous women had nationality other than Scandinavian, whereas the corresponding percentage in the total population was 5%. If immigrant status was evaluated as a risk factor, the calculated OR for DS among immigrants (after stratification for year of birth, maternal age, and parity) for all ages, <35 years, and ⩾35 years was 1.20 (1.02–1.41), 1.13 (0.93–1.38), and 1.36 (1.03–1.80), respectively. However, if the analysis of multiparity as a risk factor for DS was limited to Swedish citizens only, a statistically significant positive association between multiparity and DS remained and was of about the same magnitude as if immigrants were included. The odds ratios for DS, after exclusion of immigrants, among 5+-para for all ages, <35 years, and ⩾35 years were 1.42 (1.19–1.90), 0.99 (0.64–1.53), and 1.56 (1.28–1.90), respectively. Among immigrants, no association between grand multiparity and DS was demonstrated.

Effect of Urban or Rural Areas of Residence

One explanation for the increased risk for grand multiparous women to have an infant with DS might be that these women tend to live in rural areas, with long distances to hospitals where amniocentesis can be performed. Long distances could make these women less prone to undergo prenatal diagnosis. However, stratification for denseness of population at the community of residence did not alter the ORs shown in Table II.

Effect of Truncated 1-Year Maternal Age Classes

An analysis of variance based on exact maternal ages (in days) was carried out in order to investigate whether, within each 1-year maternal age class (30–49 years), DS mothers were older than reference mothers, and if the grand multiparous mothers were older than 1–4 parous mothers at the expected date of delivery. The difference in mean age between mothers of DS infants and controls when results from all age groups were summarized was small but statistically significant (7.0 days 95% CI: 2.9–11.1 days). The difference in mean age between Down mothers and reference mothers never exceeded 40 days within any age group. Within each of the age groups 30–39, the grand multiparas were significantly older than 1–4 paras. The difference in mean age between grand multiparous mothers and 1–4 paras within these age groups varied from 17 to 8 days. The upper limit of the 95% CI did not exceed 25 days in any group. For age groups ⩾40, the multiparous women were not significantly older than

1–4 paras within any age group. Within those age groups, the difference between the mean age among 5+ paras and 1–4 paras varied from −52 days to +36 days. Using the equations of the regression lines shown in Figure 1, the expected numbers of infants born with DS were estimated for each time period by applying the mean age among multiparas or the class mid-values, respectively. The expected number of infants with DS born in 1973–1993 to grand multiparous women if mean age or class mid-values were used in the equations were 118.5 and 118.1, respectively.

DISCUSSION

It has been speculated whether the association between grand multiparity and Down syndrome found in two previous studies [Fishman, 1994; Castilla and Paz, 1994] has been causal, an artifact arising from the truncated maternal age intervals, or due to selection bias. The effect of truncated maternal age intervals on risk estimates was investigated thoroughly in this study. Within each maternal 1-year age class, the mean ages at the expected date of delivery among DS mothers and among grand multiparous mothers were higher than corresponding mean ages among references and 1–4-parous women, respectively. However, when the effect of this truncation on the results shown in this study was evaluated, it was found that the effect was marginal.

The association between grand multiparity and DS shown in the present study was only demonstrated among women of 35 years or older, and increased during the study period, as did the opportunity to undergo prenatal diagnosis for women of this age group. This heterogeneity over strata and the fact that among parities 2–4 no tendency of any increasing risk for DS with parity could be seen definitely speaks against the hypothesis that the association between grand multiparity and DS is causal. Instead, the results support the hypothesis that grand multiparous women belong to a group of parents that are less likely to accept prenatal diagnosis and to choose termination. As no nationwide registration of prenatal diagnosis exists for the relevant time period, it was not possible to explicitly compare the rate of amniocentesis among women of parity 5+ with the corresponding rate among women of lower parity. But even if the data set used in the analysis on parity and amniocentesis was comparatively small, the negative association between grand multiparity and amniocentesis was highly significant.

The group of grand multiparous women to a large extent consists of women belonging to SEI groups 3 and 4 (workers and housewives). But as only a moderate (not significant) risk increase for workers, and no risk increase for housewives, to have an infant with DS was demonstrated, and as within each of these SEI groups an association between grand multiparity and DS was demonstrated, education level does not seem to be the major component causing an association between grand multiparity and DS. Among non-Scandinavian immigrants, no effect of parity on the incidence of DS was demonstrated, and the incidence of DS was significantly higher among these women than among Swedish citizens. A plausible explanation is that immigrants of all parities are less likely to undergo prenatal diagnosis than Swedish citizens. However, the association between grand multiparity and DS were of the same magnitude irrespective of whether immigrants were included or not.

The decreased OR shown in Table II for parity 1 could to some extent be explained by the increased OR for parity 5+, but the negative association between parity 1 and DS remained when parity groups 2–4 were used as a reference group, as shown in Table III. A decreased risk for primiparas to give birth to an infant with DS was reported previously by Källén and Måsbāck [1988] (the same sources of information as used in this study, but with a study period 1973–1983), and Stoll et al. [1990], based on 139 cases of DS. In the analysis of parity and amniocentesis in the present study, a slightly increased OR (not statistically significant) for amniocentesis among primiparas was indicated. But as the negative association between primiparity and DS was demonstrated within all age groups, it is not likely to be due to selection bias caused by differences in the probabilities to perform selective abortions among parity 1 mothers vs. mothers of parity 2–4. In the absence of demonstrable confounders, it is plausible that the negative association of primiparity and DS is causal. The mechanisms behind such an association can only be speculated on. If previous pregnancies resulted in an increased production or survival of +21 gametes, then a gradual increase with parity 2–4 in the incidence of DS would have been expected. This study showed no tendency of such an increase. Another, perhaps more plausible explanation, could be that trisomic conceptuses to primiparous mothers are more likely to be spontaneously aborted than fetuses of women with higher parities.

This study showed, with high statistical significance, an association between parity and DS. However, the results suggest that this association is a combination of (mainly) two different phenomena: 1) a decreased risk for primiparas to give birth to an infant with DS, which could have a biological explanation, and 2) an increased risk for DS in the offspring of grand multiparas, which could have a social explanation. The latter finding agrees with the conclusion of Castilla and Paz [1994] that no residual effect of grand multiparity on the incidence of DS exists in the population they studied, practically free from prenatal diagnosis and induced abortions. In Sweden, few women choose to have five children or more and probably represent a strongly selected subgroup. The results of the present study indicate that this subgroup has another attitude toward prenatal diagnosis and/or elective abortion and that this explains the increased risk for a DS infant in grand multiparas.

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